

### **REMARKS**

Applicant respectfully requests the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

#### ***Status of the Claims***

Upon entry of the present amendment, claims 1-3, 5-20, 22 and 27-29 will be pending. Claims 4, 21 and 23-26 are cancelled herein. Claims 11-15, 18 and 27-29 are currently withdrawn from consideration. Claim 16 has been amended for clarification purposes. Claim 22 is amended to depend from claim 1. Claims 1-3, 5-10, 16-17, 19-20 and 22 stand ready for further action on the merits. No new matter has been added. Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

#### ***Claim Objections***

The Examiner has objected to claims 4 and 19-22 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 4 and 21 have been cancelled herein, which renders the objection as to these claims moot.

With respect to the remaining claims, Applicant respectfully traverses the objection. Claims 19-20 further limit the "inflammatory bowel disease" recited in claim 1 to "ulcerative colitis" or "Crohn's disease." Similarly, claim 22 further limits the administration of the agent of claim 1 to "simultaneous or separate administration." Thus, Applicant respectfully requests that the objection be removed. Should the Examiner maintain the objection, Applicant respectfully requests that the Examiner provide further reasoning for the objection.

Applicant acknowledges the Examiner's statement that merely reciting the intended use of an old composition does not impart patentability thereto. However, for the reasons given below, Applicant respectfully asserts that the present invention is not an old composition.

***Issue under 35 U.S.C. § 112, second paragraph***

The Examiner has rejected claim 23 under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 23 has been cancelled herein, which renders the rejection moot.

***Issues under 35 U.S.C. § 103(a)***

The Examiner has rejected claims 1-10, 16-17 and 19-23 under 35 U.S.C. § 103(a) as being unpatentable over The Merck Manual in view of Matsuura et al. '634 (US 2004/0102634).

Claims 4, 21 and 23 have been cancelled herein, which renders the rejection as to these claims moot. With respect to the remaining claims, reconsideration and withdrawal of this rejection are respectfully requested based on the following considerations.

**Legal Standard for Determining Prima Facie Obviousness**

Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The Supreme Court of the United States has recently held that the teaching, suggestion, motivation test is a valid test for obviousness, but one which cannot be too rigidly applied. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 82 USPQ2d 1385 (U.S. 2007). The Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, *ibid.*, reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C. § 103(a). The four factual inquiries under *Graham* are:

- (a) determining the scope and contents of the prior art;

- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating evidence of secondary consideration.

*Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (U.S. 1966).

The Court in *KSR Int'l Co. v. Teleflex, Inc.*, *supra.*, did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

Even so, the Court in *KSR Int'l Co. v. Teleflex, Inc.*, *ibid.*, rejected a rigid application of the "teaching, suggestion, or motivation" (TSM) test, which required a showing of some teaching, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter to be obvious.

Further, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336, quoted with approval in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

#### Distinctions Over the Cited Art

When two medicines belonging to the same classification as each other are used in combination at the dose where each medicine shows the maximum effect, the combination's effect is unlikely to be superior to each maximum medicinal effect of the single use.

As The Merck Manual indicates, cyclosporin inhibits T-cell function (p. 311). The mode of action of sulfasalazine has not been elucidated completely. However, it is reported that the medicine shows the medicinal effect via an inhibition of cytokine production such as T-

monocyte TNF $\alpha$  production by T-monocyte or IL-2 production by T-cell and a cytokine signaling such as NF $\kappa$ B. See Gronberg A, Isaksson P and Smedegard G, Inhibitory effect of sulfasalazine on production of IL-1b, IL-6 and TNF $\alpha$ , *Arthritis Rheum* 37:S383, 1994; E.Y. Bissonnette, J.A. Enciso and A.D. Befus, Inhibitory effects of sulfasalazine and its metabolites on histamine release and TNF- $\alpha$  production by mast cells, *J. Immunol.* **156** (1996), pp. 218-223; Carlin G, Nyman AK, and Gronberg A, Effects of sulfasalazine on cytokine production by mitogen-stimulated human T cells, *Arthritis Rheum* 37:S383, 1994; C. Wahl, S. Liptay, G. Adler and R.M. Schmid. *J. Clin. Invest.* **5** (1998), pp. 1163-1174. Applicants will provide these references as well as the references cited below upon request.

There are various views on the mode of action of an inflammatory action of a PPAR $\gamma$  agonist. However, some points still remain unclear. Currently, inhibitory effect on T-cell function, an inhibition of cytokine production such as T-monocyte TNF $\alpha$  production by T-monocyte, and a cytokine signaling such as NF $\kappa$ B have been reported. See X.Y. Yang, L.H. Wang, T. Chen, D.R. Hodge, J.H. Resau and L. DaSilva *et al.*, Activation of human T lymphocytes is inhibited by peroxisome proliferator-activated receptor  $\gamma$  (PPAR)  $\gamma$  agonists, *J Biol Chem* **275** (2000), p. 4541; C. Jiang, A.T. Ting and B. Seed, PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines, *Nature* **391** (1998), pp. 82-86; M. Ricote, A.C. Li, T.M. Willson, C.J. Kelly and C.K. Glass, The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation, *Nature* **391** (1998), pp. 79-82. That is, a PPAR $\gamma$  agonist can be considered to belong to the same classification as cyclosporin and sulfasalazine. In this case, it is presumed that the combination of a PPAR $\gamma$  agonist and cyclosporin or the combination of a PPAR $\gamma$  agonist and sulfasalazine cannot achieve effects superior to the maximum medicinal effects of each medicine in single use.

Relevant to this § 103(a) rejection, *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966) has provided the controlling framework for an obviousness analysis, wherein a proper analysis under § 103(a) requires consideration of the four *Graham* factors. One such factor includes the evaluation of any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467. In this regard, Applicant respectfully submits that the present invention has achieved unexpected results, whereby such

results rebut any asserted *prima facie* case of obviousness. See *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Also, the comparative showing need not compare the claimed invention with all of the cited prior art, but only with the closest prior art. See M.P.E.P. §§ 716.02(b) and 716.02(e).

In this regard, Applicant notes M.P.E.P. § 2144.08(5)(B), which states that rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

As is clear from the Example and Tables 1 to 5 of the present specification, the combination of a PPAR $\gamma$  agonist and sulfasalazine or a PPAR $\gamma$  agonist and cyclosporin are superior to the maximum medicinal effects of each of the three medicines in single use. These effects are different from the presumption as described above. The unexpected and superior effects of a PPAR $\gamma$  agonist and sulfasalazine or a PPAR $\gamma$  agonist and cyclosporin are claimed in the present invention.

Thus, due to the unexpected results as achieved by the present invention, this rejection has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

**CONCLUSION**

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicant respectfully requests that a timely Notice of Allowance issue for the present case clearly indicating that each of claims 1-3, 5-10, 16-17, 19-20 and 22 are allowed and patentable under the provisions of title 35 of the United States Code.

In view of the above amendment, applicant believes the pending application is in condition for allowance.


Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey, Reg. No. 32,881, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§ 1.16 or 1.147; particularly, extension of time fees.

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Respectfully submitted,

By

  
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